'Moonlighting' enzyme unravels arginine paradox

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(Medical Xpress) -- Nearly 20 years ago, the journal *Science* tagged nitric oxide as the "molecule of the year." Since that time, researchers have tried to study and target this simple molecule that is involved in virtually every process of the body. However, focusing on the molecule and the enzyme directly involved in its production has proven difficult and futile.

Now, researchers at Baylor College of Medicine have not only found a way to change the production of nitric oxide in the cell, along the way, they may have solved the mystery of the "arginine" paradox. They describe their work in an article in the current issue of the journal *Nature Medicine*.

"Arginine is the single amino acid in the body that makes nitric oxide," said Dr. Brendan Lee, professor of molecular and human genetics and a Howard Hughes Medical Institute investigator at BCM. Even though there may be sufficient arginine in the cell to produce enough nitric oxide for the cell's needs, giving more arginine results in the production of more nitric oxide. That is the arginine paradox.

The paradox

"Think of it as though you were baking a cake," said Lee. "You have tons of eggs in the bakery but you can bake only so many cakes each day. You should be saturated in terms of your requirement for eggs. For

some reason, though, when a truck brings in an extra 10 cases of eggs, you make more cakes."

The answer rests with argininosuccinate lyase, an enzyme critical to making arginine – the nitric oxide precursor. Mice and people who lack this enzyme have widespread organ damage and a deficiency in nitric oxide. The patients who lack this enzyme have high ammonia levels that can damage their brains and other organs. Thankfully, there are now effective treatments that prevent the deadly build-up of ammonia. However, even without episodes of elevated ammonia, these patients have other complex, long term problems – many of which could be expected from a deficiency in nitric oxide.

Studies in mice demonstrated that without this enzyme (also called ASL) the body cannot make arginine and cannot use it either. Just giving arginine to these mice that lack the enzyme did not solve the problem with nitric oxide.

Double function

"To carry our bakery story further, this enzyme not only delivers the eggs to the bakery, it also transfers the eggs in the bakery into the blender for use in baking the cakes," said Lee. "This enzyme has two separate functions. The first is to make arginine and the second is to hold together a complex of proteins that transfers arginine inside the cell, or into the 'oven,' that makes nitric oxide. What our work suggests is that this enzyme is the central way of regulating all of nitric oxide production in the body."

A patient he treated 13 years ago sparked Lee's interest in this area. The child, who lacked this important enzyme, developed very high blood pressure at age three.

"It was unresponsive to any drugs usually used to treat high blood pressure – ACE inhibitors, calcium channel blockers, etc.," said Lee. One potential explanation for this is the central deficiency of nitric oxide in the body.

Transformative

These finding open a door into ways to explore the effect of nitric oxide on a host of disorders. Much of the work was funded by a Transformative R01 grant from the National Institutes of Health. Such grants allow research to explore new avenues in an attempt to open new doors to the understanding and treatment of disease.

"We hope it transforms the field," said Lee.

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